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iREVIEWS

FROM PICTURES TO PRACTICE PARADIGMS

Chronic Ischemic Left Ventricular Dysfunction

From Pathophysiology to Imaging and its Integration Into Clinical Practice

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Chronic ischemic left ventricular dysfunction is present in a number of clinical syndromes in which myocardial revascularization results in an improvement of left ventricular function, patients' functional class, and their survival. Early diagnosis of and treatment of viability is essential. Coronary arteriography is of limited value in diagnosis of viability. Noninvasive testing is essential for diagnosis, which can be matched to the pathophysiologic changes that occur in hibernating myocardium. However, no single test has a perfect, or near perfect, sensitivity and specificity, and thus, a combination of tests are usually needed. Algorithms are developed to integrate these tests in clinical decision making. (J Am Coll Cardiol Img 2008;1:536–55) © 2008 by the American College of Cardiology Foundation

Scientific discoveries tend to be made not by those who seek to prove a hypothesis, but by those who keep their eyes open . . .

Isaac Newton
Albert Einstein (1)

It was believed that left ventricular (LV) dysfunction (LVD) at rest was the result of ongoing ischemia or myocardial infarction. Thirty-three years ago, studies of patients undergoing coronary artery bypass graft surgery for angina led to the discovery of improvement or even normalization of the LVD with myocardial revascularization; that is, there was viable myocardium (hibernating myocardium [HM]) in areas of LV dysfunction (2,3). It took about 12 years for the concept of HM to be clinically acceptable. In the ensuing years, certain clinical issues have been recognized:

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- Hibernating myocardium has been documented in a number of clinical syndromes besides angina (stable/unstable). These include acute myocardial infarction, LV aneurysm, heart failure, aborted sudden death, anomalous left coronary artery from the pulmonary artery, and valve disease with LV dysfunction.
- Revascularization of HM results in an improvement of regional and global LV systolic function (4), remodeling is reversed (5,6), survival is increased (7), and there is a decrease of the composite of myocardial infarction, heart failure, and unstable angina (8). Importantly, revascularization of LVD in the absence of significant amounts of viable myocardium was not of demonstrable beneficial clinical effects (7).
- The lumen of the vessel distal to a severe coronary obstruction is related to disease of the vessel as well as to the amount of myocardial blood flow (MBF). After revascularization, the lumen may increase depending on the increase of MBF (2). The ability to judge the amount of MBF from a coronary arteriogram is limited. Moreover, when the reduction in MBF is large at rest, even a "small" increase of MBF with revascularization may improve patient outcomes but to a greater degree (Table 1).
- One vessel disease can also result in changes in the remote areas without associated coronary artery disease. The remote areas show: 1) reduced coronary vasodilator reserve and altered metabolism (9); 2) histological changes similar to those seen in areas of HM in an experimental study with left anterior descending artery stenosis (10); and 3) improvement/normalization of LV function after revascularization of the areas of HM with left anterior descending coronary artery occlusion (6).
- About two-thirds of patients with heart failure in the developed world have underlying coronary artery disease, and these patients have a significantly worse prognosis than patients with nonischemic heart failure (11). In the CHRISTMAS (Carvedilol Hibernating Reversible Ischaemia Trial), 29% of patients had HM and 19% had reversible perfusion defect (12); these patients had greater improvement of LV function.
- Early revascularization of HM is associated with greater improvement of LV function (7) and also of patient survival (13).
- There are major limitations to diagnosing HM by invasive techniques.

These findings have emphasized the need for and importance of noninvasive tests to diagnose and quantitate the viable myocardium in areas of LV dysfunction.

This review is limited to assessment of myocardial viability only in *chronic* LVD and will not attempt to differentiate between stunning and hibernation. It will focus on the important issues for the noninvasive cardiac imager, namely: 1) pathophysiology of myocardial hibernation as it pertains to the imager and imaging targets; 2) identification of viable myocardium and prediction of functional outcomes by various imaging modalities; 3) integrated imaging schema that can be used in the clinical setting to identify a viable myocardium; and 4) issues involved in clinical decision making.

ABBREVIATIONS AND ACRONYMS

ATP = adenosine triphosphate
BMIPP = beta-methyl-p-[^{123}I]-iodophenyl-pentadecanoic acid
CFR = coronary flow reserve
CMR = cardiac magnetic resonance
CR = contractile reserve
FDG = fluorodeoxyglucose
HM = hibernating myocardium
LDDE = low-dose dobutamine echocardiography
LGE = late gadolinium enhancement
LV = left ventricular
LVD = left ventricular dysfunction
LVEF = left ventricular ejection fraction
MBF = myocardial blood flow
MI = myocardial infarction
PET = positron emission tomography
SE-MBF = subendocardial MBF
SPECT = single-photon emission computed tomography
TM-MBF = transmural MBF

Pathophysiology of Chronic LVD

Flow-function alterations. EXPERIMENTAL STUDIES. The fundamental derangement is reduced MBF, specifically subendocardial MBF (SE-MBF). In normal animals, the subendocardium governs transmural contraction and the subendocardium receives more MBF per unit of muscle than the epicardium (14) (Table 2). In conscious dogs, there is a sensitive coupling between SE-MBF and function so that only a 20% reduction in SE-MBF (15) can cause severe regional dysfunction, and the relationship between systolic thickening and SE-MBF is more or less linear and dependent on the hemodynamic situation (16). There is a 2 to 1 relationship in the reduction of SE-MBF to reduction of transmural MBF (TM-MBF) (16–19). For example, a 25% reduction in TM-MBF results in a 50% reduction in SE-MBF (Fig. 1). A 50% reduction in TM-MBF in an anesthetized dog (20) and 75% reduction in SE-MBF in the conscious dog results in akinesis of the LV wall; whereas subepicardial MBF does not correlate to transmural LV wall function (14). In animals with coronary arterial obstruction following relief of ischemia, the ischemia-induced vasodilation is maldistributed in the myocardium supplied by the obstructed coronary artery, possibly due to microcirculatory changes. As a result, the increased volume of MBF from the hyperemia is directed to a greater extent to the epicardium and the subendocardium remains

Table 1. Suggested Change in Patient Outcomes With the Same Increase of MBF in 2 Different Clinical Situations

Clinical Situation	Changes After Revascularization: MBF Before	MBF After	Increase of MBF	CCVS Angina Class Before	CCVS Angina Class After	NYHA Functional Class Before	NYHA Functional Class After
A	100	130	30	II	0 to I	II	I
B	30	60	30	IV	I to II	IV	II

CCVS = Canadian Cardiovascular Society; MBF = myocardial blood flow (ml/min/100 g of muscle); NYHA = New York Heart Association.

ischemic at least for a period of time (21). Thus, relief of ischemia and even restoration of TM-MBF does not necessarily mean SE-MBF is normal or has been restored to pre-ischemic levels.

Some studies of acute and short-term cardiovascular manipulations in animals have shown that episodes of ischemia lead to the development of HM (22).

Experimental studies of adaptation to chronic fixed coronary stenosis have shown: 1) MBF may be normal or only mildly diminished in the early period but regional contraction may already be reduced (stunning), but over the subsequent period, reduction in MBF and function are matched (hibernation) (14,23); and 2) progression to matched decreases in flow and function (HM) also occurs very early when a 15-min partial coronary occlusion is followed by reperfusion through a critical stenosis (hibernation) (10).

CLINICAL STUDIES. The few studies that showed that blood flow was "not reduced" measured only TM-MBF by positron emission tomography (PET); at that time, it was not possible to measure SE-MBF in humans. The weight of evidence shows that patients with HM have reduced TM-MBF at rest (14), which implies SE-MBF is significantly reduced to a much greater extent.

Until recently it was not possible to measure SE-MBF in humans with any degree of precision. Using cardiac magnetic resonance (CMR) imaging, Selvanayagam et al. (24) have documented in patients with HM that SE-MBF is reduced at rest when compared with areas without significant coronary stenosis in the same patients, and following revascularization, SE-MBF and LV function are normalized/improved (Fig. 2). This led Klocke (25) to conclude that this study "provides convincing evidence for the hibernation paradigm" (25).

CORONARY FLOW RESERVE. Coronary flow reserve (CFR) is reduced in people with hyperlipidemia, in those with coronary atherosclerosis, and in patients with obstructive coronary artery disease. Thus, reduced CFR is not just a phenomenon of HM or stunning.

Irrespective of rest flow, CFR is almost always reduced in viable but dysfunctional myocardium, albeit more severely in segments with low flow at rest. The severity of CFR reduction directly has an impact on the ability of viable myocardium to improve its contraction upon inotropic stimulation, as this requires increases in MBF. Viable segments without contractile reserve (CR) usually have lower CFR than viable segments with CR do. The response of viable segments to these stimuli varies greatly from segment to segment as well as with the intensity and the duration of stimulation. Many viable segments in HM exhibit a biphasic response when challenged by increasing levels of inotropic stimulation (26). At low levels of stimulation, and provided that sufficient CFR is present, systolic wall thickening usually increases and starts earlier in systole. At higher levels, when the increase in demand cannot be matched anymore by further increases in MBF, systolic function again deteriorates and can even become worse than at baseline. The observation of this biphasic pattern is impor-

Table 2. Pathophysiology of Coronary Blood Flow

- In normal animals:
  - SE-MBF governs transmural contraction
  - SE-MBF is greater than epicardial MBF
- In animals with coronary artery obstruction there is:
  - Sensitive coupling between SE-MBF and contraction
  - A 2 to 1 relationship between reductions of SE-MBF and of reduction TM-MBF
  - A 50% to 75% reduction of SE-MBF results in left ventricular akinesis
  - After relief of an ischemic episode the hyperemia due to vasodilation is maldistributed so that SE-MBF is still reduced for a period of time
- In humans with hibernating myocardium:
  - SE-MBF is reduced
  - Coronary flow reserve is reduced*

*It is also reduced in normal people, and patients, with significant coronary atherosclerosis.
SE-MBF = subendocardial myocardial blood flow; TM-MBF = transmural myocardial blood flow.

tant to rule out other causes of regional dysfunction such as the presence of a subendocardial scar or remodeled myocardium, both of these conditions being characterized by a sustained CR at both low and high levels of inotropic stimulation. About 20% to 25% of viable segments do not improve functionally during inotropic stimulation. These segments usually have mild reduction of resting MBF, avidly take up glucose under fasting conditions, and have an almost completely exhausted MBF reserve. A low MBF reserve prevents the segments from increasing their oxygen consumption upon inotropic stimulation and hence from increasing their contractile functions. Apart from the exhaustion of MBF reserve, other factors, such as the presence and severity of cardiomyocytic alterations or down-regulation of beta-adrenoreceptors, may also contribute to the lack of CR in apparently viable segments.

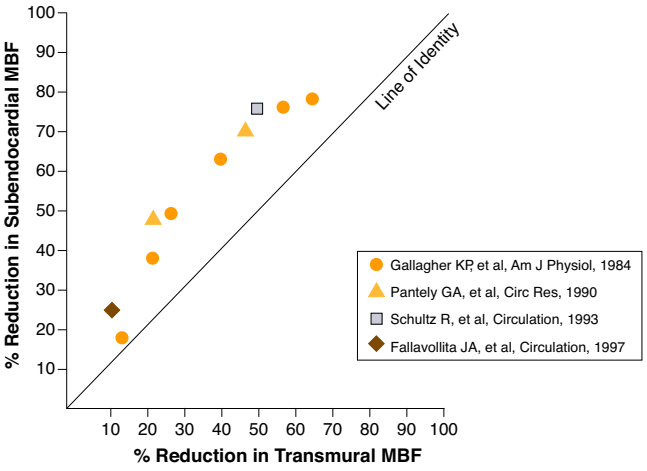

Figure 1. Relationship of SE-MBF to TM-MBF With Reductions of Transmural Blood Flow

Reduction of subendocardial myocardial blood flow (SE-MBF) is shown on the vertical axis and transmural myocardial blood flow (TM-MBF) on the horizontal axis. For 25% to 50% reduction of TM-MBF, the SE-MBF is reduced by 50% to 75%. Data from experimental studies were adapted and/or calculated from Gallagher et al. (16), Pantely et al. (17), Schulz et al. (18), and Fallavollita et al. (19), with permission.

Structural Alterations in LVD

Besides the changes in resting MBF and CFR, several structural alterations affect cardiomyocytes and extra cellular matrices in patients with chronic HM (22,27). These structural changes are mostly encountered in the areas of dysfunction, but can also be seen in remote normally contractile regions. Most of the available information on these structural changes has been gathered from studies in which human myocardial biopsy specimens were harvested at the time of coronary bypass surgery and also from experimental studies of HM.

Microcirculation. Histological analysis of human dysfunctional myocardium demonstrated that the microvasculature was better preserved in segments that improved in function after revascularization than in those that remained dysfunctional. This is particularly true for the capillaries whose density and cross-sectional area are usually within the normal range in viable segments (28). In contrast, there is greater heterogeneity among persistently dysfunctional segments despite revascularization, and approximately half of them show significant capillary rarefaction.

Myocytes. The primary *alteration* is the depletion of contractile elements in the cardiomyocytes. In some cells, this is limited to the vicinity of the nucleus; whereas in others it is very extended, leaving only few or no sarcomeres at the cell periphery. The space previously occupied by the myofilaments is usually filled with glycogen. The mitochondria are increased in number and display alterations in size and shape. Nuclei are usually tortuous and show uniformly dispersed heterochromatin. Sarcoplasmic reticulum is virtually absent, as are T tubules. At the molecular level, the expression of myosin, actin, titin, and alpha-actinin is usually reduced. Cytoskeletal proteins such as desmin, tubulin, and vinculin are disorganized. The expression of connexin 43, a major gap junction protein, and that of nuclear A-type lamins are also reduced.

Extracellular matrix. The extracellular matrix shows increased amounts of type I collagen, type III collagen, and fibronectin in chronic LVD. Within the widened interstitium, an increased number of vimentin-positive cells (endothelial cells and fibroblasts) and macrophages can usually be seen.

The severity of the structural changes that affect a chronically dysfunctional myocardium are likely to impact on its ability to respond to an inotropic stimulus and on the speed at which it may or may not recover after revascularization. Segments with less fibrosis or with less severe cardiomyocytic alterations are more likely to improve in function following the administration of dobutamine or after revascularization. Current data suggests a spectrum of myocardial dysfunction may exist in patients with coronary artery disease.

Pathophysiological Targets for the Imager

Based on the understanding of the pathophysiology of myocardial viability, a number of these targets

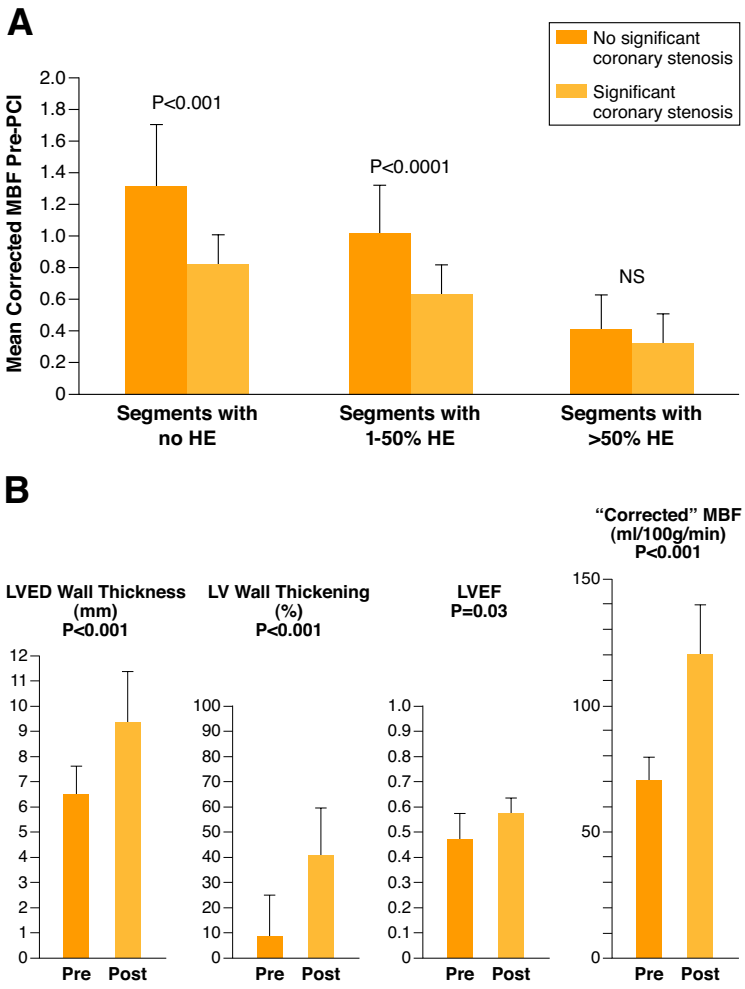

Figure 2. Relationship of Mean Corrected SE-MBF to Transmural Grade of Myocardial Hyperenhancement

Relationship of mean corrected myocardial blood flow (MBF), that is SE-MBF, to transmural grade of myocardial hyperenhancement (HE) before percutaneous coronary intervention (PCI) is shown **(A)**. Comparison is made between segments subtended by stenosed and non-stenosed coronary arteries ($p > 0.05$ is not significant). In **panel B**, pre- and post-PCI data are shown in **dark orange** and **light orange**, respectively, for left ventricular end-diastolic (LVED) wall thickness, left ventricular (LV) wall thickening, left ventricular ejection fraction (LVEF), and corrected SE-MBF. Figure drawn from data of Selvanayagam et al. (24), with permission. Abbreviation as in Figure 1.

can be clinically imaged. The following section describes each of the imaging techniques that can be used to image the key pathophysiologic substrates of: 1) fibrosis and/or cellular viability; 2) flow-metabolism; 3) microcirculation; and 4) CR.

Assessment of Fibrosis and/or Cellular Viability

The most important determinant of the return of resting contraction following revascularization is the severity of the underlying tissue fibrosis, and whether it is interstitial or infarct-related. Imaging methods such as delayed enhancement–CMR, thallium and metabolic imaging using PET, echocardiography, and CMR can directly assess the presence of tissue fibrosis, the mass of viable cardiomyocytes, or the consequences of fibrosis such as wall thickness/chamber size. However, in the absence of flow or CR measurements, images obtained at rest, although sensitive, cannot distinguish between viable and remodeled myocardium (especially in the remote myocardium) and therefore lack specificity.

Echocardiography. SPATIAL EXTENT OF LV SCARRING. The LV volume measurement is a guide to the degree of irreversible LV damage. A very dilated LV (end-diastolic volume greater than twice the upper limit of normal) is unlikely to demonstrate significant global functional recovery (e.g., improvement of LV ejection fraction [LVEF] >5%), as this

degree of LV remodeling is usually caused by a large number of scarred segments. A 2-dimensional echocardiography underestimates LV volumes, but LV opacification improves the reliability of these measurements. A 3-dimensional echocardiography permits more accurate volume measurements without needing to make geometric assumptions, which is desirable if the LV has been involved in multiple previous myocardial infarctions (29).

The involvement of >4 ventricular wall segments by scarring (i.e., thinned segments) also identifies the LV that is unlikely to show global functional recovery after revascularization. Extensive infarction also reduces LV compliance, producing a restrictive filling pattern. A short mitral E-wave deceleration time is associated with a small number of viable segments or a large number of scar segments, and deceleration time is directly related to the degree of LVEF change after revascularization, with >5% improvement being unusual with a deceleration time of <180 ms (30). Segments with significant transmural extent of infarction become retracted and fibrotic as the infarct heals. A LV end-diastolic wall thickness of ≤0.5 to 0.6 cm is associated with akinesis or even dyskinesia, and these segments usually demonstrate no CR in response to dobutamine (30,31). A thinned segment is very unlikely to recover (≤5% probability to recover); thinning to ≤0.5 to 0.6 cm has a sensitivity of 94% for infarction but its specificity is much lower. A segment of >0.5 to 0.6 cm may recover (specificity 48%) and is more likely to do so if it augments in response to dobutamine; the combination of wall thickness with augmentation at dobutamine stress gives a sensitivity of 88% and specificity of 77% for prediction of functional recovery (30,31). Dobutamine stress and single-photon emission computed tomography (SPECT) provide similar degrees of additional information to wall thickness (31).

TRANSMURAL EXTENT OF SCARRING. Increasing transmural extent of scarring is inversely related to the likelihood of functional recovery after revascularization and correlates with the degree of reduction of radial function. Wall motion scoring is too insensitive to distinguish minor gradations of function. The thickness of a subendocardial scar may be identified using myocardial contrast echocardiography; the relative thickness of a scar and perfused myocardium corresponds with transmural extent of scarring by magnetic resonance imaging. New echocardiographic indices of LV deformation are sensitive to the reductions in function caused by nontransmural scarring. Tissue velocity-based longitudinal strain and strain rate are reduced with subendocardial scarring, although the relationship is nonlinear because of the importance of the subendocardium to longitudinal function. Studies using speckle-based (2-dimensional) strain (32) have shown radial or circumferential strain to be impaired in proportion to the transmural extent of scarring.

DIRECT EVIDENCE OF VIABILITY FROM RESTING IMAGES. Myocardial deformation is impaired in proportion to the extent of myocardial fibrosis, so the magnitude of strain is an index of the amount of chronically dysfunctional tissue. Unfortunately, this association is not sufficiently robust to be used in decision making, probably because the parameters are load-dependent. Although tissue velocity is less useful than strain for the assessment of regional changes because it is less site-specific and influenced by tethering of adjacent segments, its high temporal resolution (especially using pulsed-wave Doppler) may allow the measurement of pre-ejection velocity, which may be a load-independent marker. Preserved pre-ejection velocity has been reported to be a reasonable resting marker of viability and is a predictor of the likelihood of functional recovery and favorable outcome (33).

Magnetic resonance imaging. LATE GADOLINIUM ENHANCEMENT. Gadolinium chelates are extracellular/interstitial contrast agents that enhance T_1 relaxation in regions of infarction as a consequence of the increased volume of distribution of the chelates within a collagenous scar and their delayed washout due to reduced capillary density (34). The end result is that regions of myocardial infarction (MI) appear bright on inversion recovery images acquired 10 to 20 min after gadolinium administration. The spatial extent of late gadolinium enhancement (LGE) closely mirrors the distribution of myocyte necrosis early after MI and that of collagenous scarring seen at 8 weeks (35). Furthermore, studies have shown that in regions of the heart subjected to reversible injury, the retention of contrast does not occur (36). Regions of a chronically dysfunctional myocardium often consist of an admixture of reversibly injured and irreversibly injured (infarcted) myocardium (37). The power of LGE resides in its ability to distinguish these 2 states within the same segment of myocardium (Fig. 3).

The ability of LGE to identify and characterize myocardial scarring has been directly compared with both SPECT and PET. In a study of 91 patients with suspected or known coronary artery

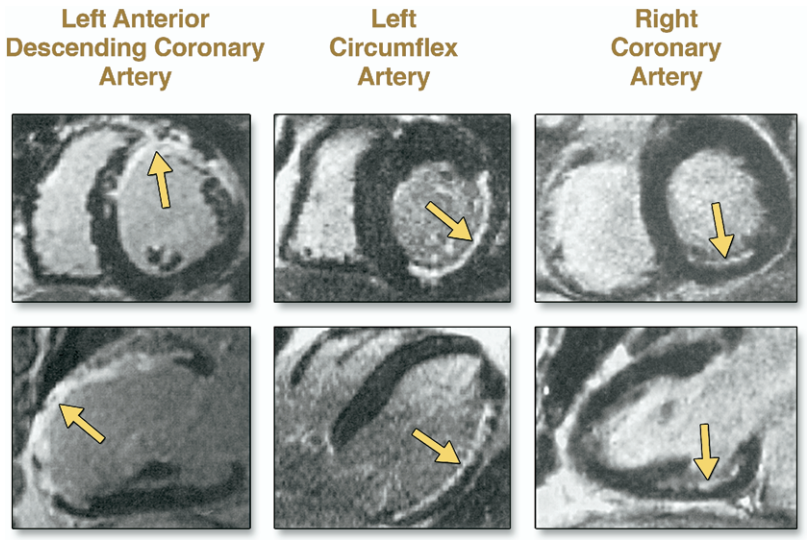

Figure 3. Contrast-Enhanced Images Obtained by MRI in Chronic LVD

Late gadolinium-enhanced images are shown in a short-axis view **(upper panels)** and a long-axis view **(lower panels)** in 3 patients. Hyperenhancement is present **(arrows)** in various coronary-perfusion territories—the left anterior descending coronary artery, the left circumflex artery, and the right coronary artery—with a range of transmural involvement. Reprinted, with permission, from Kim et al. (41). LVD = left ventricular dysfunction; MRI = magnetic resonance imaging.

disease, SPECT failed to correctly identify nearly half of the subendocardial infarcts that were identified by LGE (38). Another study (39) compared LGE to PET in 31 patients with ischemic heart failure. Infarct mass correlated well between the 2 modalities ($r = 0.81$, $p < 0.0001$), but LGE more frequently identified subendocardial scarring than PET did, again reflecting its superior spatial resolution. In fact, when the transmural extent of scarring is <37%, PET defines the segment as viable due to the presence of sufficient signal from remaining viable mid-wall and subepicardium (40). When a scar is >37% transmural, PET defines the segment as nonviable.

The utility of LGE for identifying the likelihood of functional recovery after revascularization was demonstrated in a study of 50 patients imaged before and after revascularization (41). Eighty percent of patients had some region of LGE with a mean signal intensity that was 530% of that seen in normal segments. Functional recovery inversely correlated with the transmural extent of scarring. In segments with no LGE, 78% demonstrated recovery of function. Only 1 of 58 segments with >75% transmural extent, however, showed any improvement following revascularization, thus demonstrating the powerful negative predictive value of this finding. Several subsequent studies (42,43) have further supported the LGE imaging approach for predicting functional recovery.

The standard CMR pulse sequence used for LGE imaging is an inversion recovery gradient echo technique (44) that has been carefully validated in a canine model. This pulse sequence requires selection of an inversion time that optimally nulls normal myocardium. A recently developed phase-sensitive inversion recovery technique (45) is less sensitive to the choice of an incorrect inversion time and may therefore be more efficient. Additional novel approaches include a subtractive inversion recovery technique using both a long and short inversion time (46) that improves infarct-blood pool contrast by 247 ± 136% compared with magnitude inversion recovery while maintaining signal difference-to-noise ratio for an infarct myocardium. However, subtraction techniques are prone to misregistration. Another approach to improve the differentiation of the blood pool and infarcted subendocardium is a multicontrast method using a combination of T_1- and T_2-weighted imaging (47). For patients who cannot hold their breath, a single-shot subsecond technique (48) was recently validated with slightly lower sensitivity and overall accuracy but still quite useful in the acutely ill patient nonetheless.

END-DIASTOLIC WALL THICKNESS AND RESIDUAL RIM OF VIABILITY. Studies with both echocardiography and cine CMR have established end-diastolic wall thickness as an important parameter in the assessment of myocardial viability, although its accuracy, using fluorodeoxyglucose (FDG) PET as the reference standard, is less than that of CR in response to dobutamine (49). In 1 study (50), segments that failed to improve following revascularization had a significantly lower end-diastolic wall thickness (6 mm vs. 9.8 mm, $p < 0.001$) than those that showed functional improvement. More important than end-diastolic wall thickness alone may be the residual thickness of the unenhanced rim of viable myocardium beyond the area of LGE in the subendocardium. One study (40) compared end-diastolic wall thickness and viable rim with FDG PET in a group of 22 patients with ischemic cardiomyopathy. Receiver-operator characteristic analysis demonstrated greater area under the curve for viable rim compared with end-diastolic wall thickness (0.95 vs. 0.86, respectively). Optimal cutoff values for viability were 5.4 mm for end-diastolic wall thickness and 3.0 mm for the viable rim.

RADIONUCLIDE IMAGING: SPECT. Tracers used with SPECT or PET to image MBF are commonly referred to as "perfusion tracers," because their uptake and retention mechanisms require viable myocellular membranes. Thus, uptake and visualization of myocardial regions with perfusion tracers require the presence of working, viable myocytes. This information is the converse of direct and indirect fibrosis imaging by echocardiography and CMR. Thallium-201 redistribution, which reflects myocardial potassium space with SPECT, and rest sestamibi imaging (with or without nitrates), which reflects mitochondrial membrane integrity are the 2 most common perfusion tracers used to image cellular viability.

The evaluation of myocardial ischemia and viability by thallium scintigraphy has occupied a rather unique place in the management of patients with known or suspected coronary artery disease since the late 1970s (51,52). Like potassium, thallium is transported across the sarcolemma membrane via the sodium-potassium adenosine triphosphatase system. The initial extraction and distribution of thallium in the myocardium is primarily a function of blood flow (either during stress or at rest) and is unaffected by hypoxia, chronic hypoperfusion (hibernation), or post-ischemic dysfunction (stunning), unless myocardial infarction is present. The later distribution of thallium (3 to 4 h or 24 h after stress or rest injection), termed *redistribution phase*, is flow-independent and is a function of regional blood volume and myocardial potassium space reflecting cellular viability (52,53). Thus, thallium defects on early rest images that "fill-in" on delayed, redistribution phase (termed *reversible defect*) represents a scintigraphic pattern of HM. In contrast, because thallium is not actively taken up in regions of scarred myocardium, defects on rest images that persist on redistribution images (termed *irreversible* or *fixed defect*) represent scarred myocardium.

There are a number of thallium protocols that are used clinically for the detection of myocardial viability. Among the range of choices, 2 protocols are optimized for viability detection: 1) rest-redistribution and 2) stress-4 h-redistribution-reinjection imaging (Fig. 4). The former assesses myocardial viability alone (54,55), and the latter assesses myocardial ischemia and viability (56,57). A pooled analysis of rest-redistribution and stress-redistribution-reinjection thallium studies (58,59) reported a relatively high sensitivity (80% to 90% range) and modest specificity (54% to 80% range) for the prediction of recovery of regional function after revascularization. However, these conclusions must be viewed in the context of the limitations of pooled data analysis. When taking into consideration regions with reversible defects (ischemia) and success of revascularization (reexamining regional perfusion or vessel patency after revascularization), stress-redistribution-reinjection thallium imaging yields

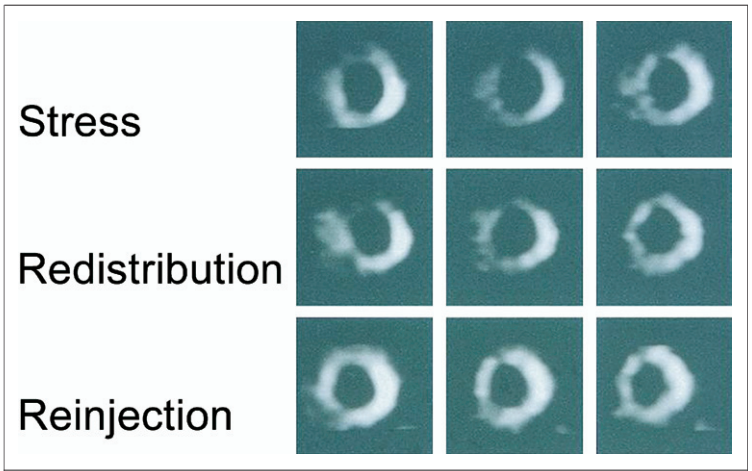

Figure 4. Thallium-201 Imaging for Myocardial Viability

Short-axis ^{201}thallium tomograms during stress **(top row)**, redistribution **(middle row)**, and reinjection **(bottom row)** imaging in a patient with coronary artery disease. There are extensive ^{201}thallium abnormalities in the anterior and septal regions during stress that persist on redistribution images but improve markedly on reinjection images. Reprinted, with permission, from Dilsizian et al. (56).

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excellent positive and negative predictive accuracy (both in the 80% to 90% range) for recovery of function after revascularization (56,57).

In the case of technetium-99m–based perfusion tracers, both sestamibi and tetrofosmin are lipophilic cationic complexes that are retained within the mitochondria due to a large negative transmembrane potential. Because accumulation and retention of sestamibi and tetrofosmin are related to energy-dependent processes that maintain mitochondrial membrane polarization, they may also serve as markers of cellular viability. The administration of nitrates to improve resting MBF prior to injection of sestamibi or tetrofosmin appears to improve slightly the ability of these tracers to detect cellular viability (60).

With regard to prediction of improvement in LV function after revascularization, both thallium and technetium-99m–based techniques have been shown to be reasonably accurate. Reported sensitivities (58,59,61) for recovery of ventricular function are in the 75% to 85% range, with positive- and negative-predictive values of about 70% and 90%, respectively. With additional enhancements to imaging protocols, such as nitrate-enhanced rest perfusion imaging and gated SPECT for assessment of function, the accuracy of these techniques is even higher (60,62).

Assessment of Flow-Metabolism Relationship

Viable myocardial segments display a variety of perfusion patterns.

Radionuclide imaging: PET. Decreased regional myocardial tracer uptake at rest could reflect either lack of cell membrane integrity in an area of scarred myocardium or reduced MBF secondary to HM (dysfunctional but viable). Therefore, in patients with chronic ischemic LV dysfunction, myocardial perfusion tracers alone may not reliably differentiate hibernating from scarred myocardium. In that setting, flow-independent probes that assess intact cellular metabolic processes may be used as an adjunct to resting myocardial blood flow.

^{18}F-2-FLUORO-2-DEOXYGLUCOSE. Despite the excellent flow kinetics and biological properties of thallium, attenuation of photons is a potential limitation for thallium in patients with large body habitus. Positron emission tomography systems have generally better sensitivity and spatial resolution than SPECT systems and provide more accurate attenuation correction. Thus, metabolic imaging with FDG PET may provide incremental information to thallium regarding myocardial viability, especially in patients with severely impaired LVD (63). High-energy phosphates, such as adenosine triphosphate (ATP), are generated in the myocardium by oxidative phosphorylation and glycolysis. In the normal myocardium, use of free fatty acids is the preferred metabolic pathway for ATP production. In the setting of myocardial ischemia, where local oxygen supply is reduced, the myocardium shifts ATP production from fatty acid metabolism (which occurs in the mitochondria and is oxygen-dependent) to glucose use (which occurs in the cytoplasm and is oxygen-independent).

The principle of using a metabolic tracer for assessing myocardial viability is based on the concept that viable tissue is metabolically active, and scarred tissue is metabolically inactive. The glucose analogue FDG may be preserved or increased in hypoperfused but viable myocardium, termed *metabolism-perfusion mismatch* (Fig. 5) (64). Conversely, FDG uptake will be decreased or absent in hypoperfused and scarred myocardium, termed *metabolism/perfusion match.* The metabolism-perfusion mismatch pattern represents a scintigraphic marker of HM. The PET imaging in dysfunctional myocardium had positive and negative predictive values of 85% and 92%, respectively, for recovery of function after revascularization (65–71). A subsequent European multicenter trial (72) in 178 patients confirmed the high sensitivity of PET mismatch pattern for predicting functional recovery after revascularization.

The prognostic significance of perfusion-metabolism mismatch pattern has been demonstrated in several nonrandomized, retrospective studies with PET. Patients with perfusion-metabolism mismatch pattern (HM) who were treated with revascularization had lower ischemic events and deaths when compared with those treated medically (7,73,74). Moreover, the extent of the PET mismatch pattern correlated with improvement in LV function, clinical course, and magnitude of heart failure symptoms after revascularization (75). Patients with matched defects (concordant reduction in regional perfusion and metabolism), indicating a scarred myocardium, displayed no such difference in outcomes or clinical benefit from revascularization (7).

The principal limitation for the widespread application of PET imaging for the assessment of myocardial metabolism is its availability. Currently

in the U.S., there are approximately 1,600 PET cameras versus 12,000 SPECT cameras. Thus, PET is not readily available for most practicing cardiologists. Because SPECT cameras are more prevalent than PET cameras in the community and cardiology offices, investigators have recently focused their attention on developing gamma-emitting metabolic radiotracers, such as beta-methyl-p-[^{123}I]-iodophenyl-pentadecanoic acid (BMIPP), to make the assessment of myocardial metabolism readily available to patients presenting with symptoms of heart failure or LVD (76).

BETA-METHYL-P-[^{123}I]-IODOPHENYL-PENTADECANOIC ACID. BMIPP is a fatty acid analogue that provides insight into myocardial metabolism using SPECT cameras. In a recent study, delayed recovery of myocardial metabolism after ischemic injury, termed ischemic memory, was shown with BMIPP (75). Fatty acid metabolism remained suppressed for a prolonged time (up to 30 h following an ischemic episode) even after perfusion had returned to normal (76,77).

Uptake of BMIPP from the plasma into myocardial cells occurs via CD36 transporter protein present on the sarcolemma membrane. Retention of BMIPP in the myocardium most likely reflects activation of fatty acids by coenzyme A, and indirectly, of cellular ATP production resulting from fatty acid metabolism. Thus, in the setting of myocardial ischemia, reduction in ATP production secondary to diminished fatty acid metabolism is mirrored by decreased myocardial BMIPP uptake. Although BMIPP is approved for clinical use in Japan, it has not yet received approval by the Food and Drug Administration in the U.S. In the clinical setting, the finding of persistent and prolonged disturbances in BMIPP uptake, long after resolution of ischemic symptoms, may provide a scintigraphic imprint as to the underlying cause of chronic LVD.

Assessment of Microcirculation

Contrast echocardiography. The coronary microcirculation is preserved in myocardium with chronic ischemic LVD. The microbubbles in echocardiographic contrast agents are intravascular tracers and the intensity of their reflected signal can be used to demonstrate the presence and relative size of the microcirculation, and their rate of accumulation related to coronary flow. Myocardial contrast enhancement of dysfunctional segments at rest is therefore a potential marker for viable myocardium. The value of contrast echocardiography for this has been reported in over 10 studies, with sensitivities ranging from 62% to 92%, and specificity from 67% to 87%. Nonetheless, this technique remains technically challenging and may be difficult to use in all myocardial segments due to issues of shadowing and attenuation.

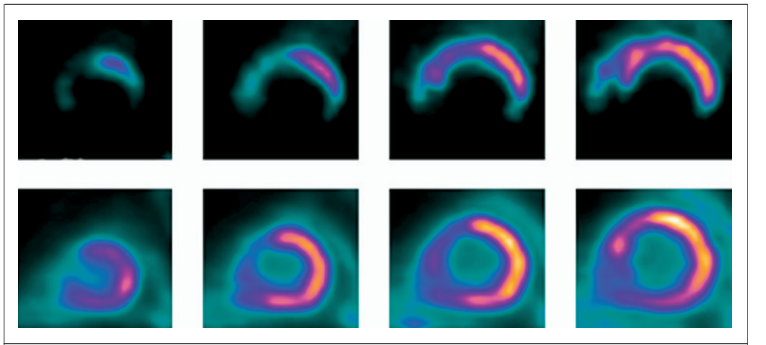


Figure 5. PET Imaging and Perfusion-Metabolism Mismatch in Hibernation

Positron emission tomography (PET) scan showing perfusion **(top)** to metabolism **(bottom)** mismatch in hibernating heart as an example of preserved cardiometabolic reserve. Rubidium-82 PETs in short-axis view **(top row)** show markedly decreased perfusion defects in the apical, inferior, inferolateral, and septal regions of the left ventricle at rest, which extends from distal to basal slices. [^{18}F] 2-deoxy-2-fluoroglucose images acquired under glucose-loaded condition **(lower row)** show perfusion-metabolism mismatch pattern (the scintigraphic hallmark of hibernation) in all abnormally perfused myocardial regions at rest, with the exception of the anteroseptal region, which demonstrates matched perfusion-metabolism pattern (compatible with scarred myocardium). Reprinted, with permission, from Taegtmeyer and Dilsizian (64).

Assessment of CR

Resting scar imaging and perfusion imaging does not permit distinction between viable and remodeled myocardium. Assessment of MBF or CR is therefore mandatory combined with perfusion, metabolic, or scar imaging.

Dobutamine stress echocardiography. Viable myocardium has been shown to augment function in response to inotropes (e.g., dobutamine, amrinone), coronary vasodilators (e.g., dipyridamole), arterial vasodilators (e.g., levosimendan), and low level of exercise. However, the most widely used stressor to augment function is low-dose dobutamine echocardiography (LDDE), with an average sensitivity of 75% to 80% and a specificity of 80% to 85% for the prediction of functional recovery both early after infarction as well as in the setting of chronic LVD. Augmentation of function in response to low-dose dobutamine is a more reliable predictor of recovery than improvement at peak dose (e.g., 40 μg/kg/min). Nonetheless, the peak-dose response is important, because the most reliable predictor of functional recovery is the biphasic response (i.e., augmentation at low dose with deterioration at peak dose) indicating that the tissue is not only viable but

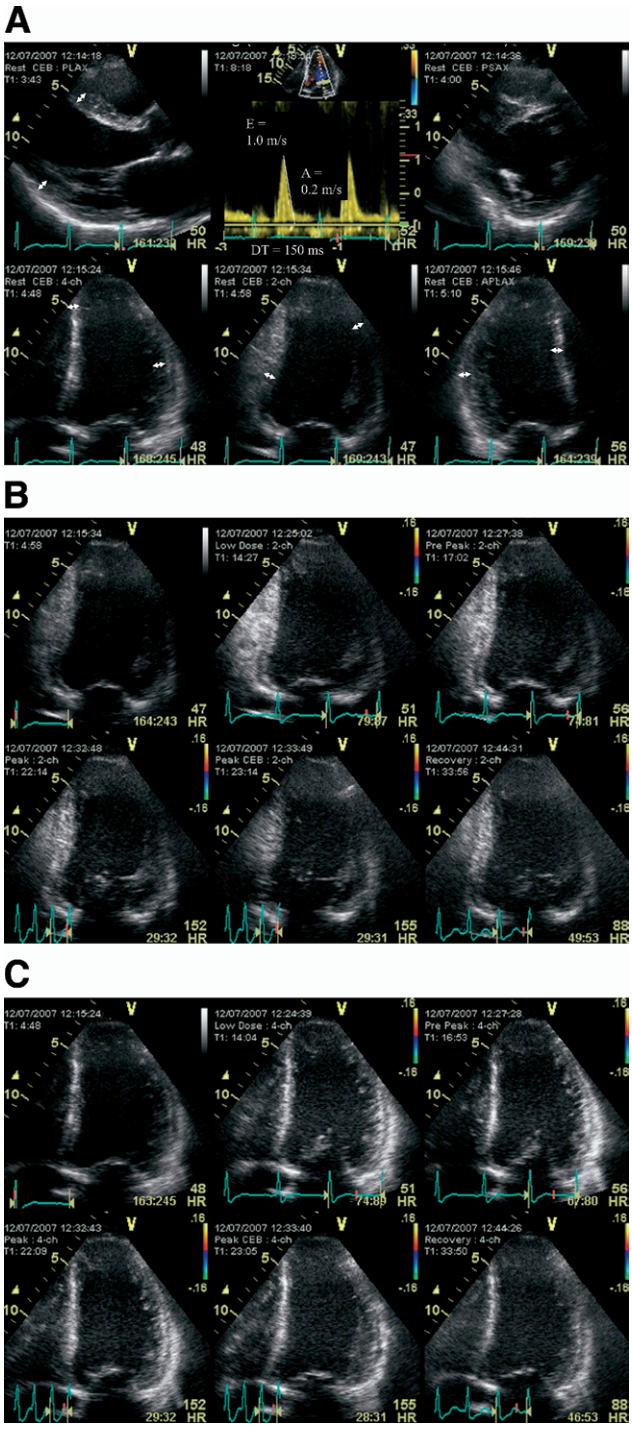


Figure 6. Resting and Dobutamine Stress Echo for Myocardial Thinning, CR, and Myocardial Ischemia

Integration of resting data and new technologies predicts functional recovery in a patient with severe dysfunction (LVEF 25%). The resting study **(A)** shows no areas of thinning (1-cm markers in all walls) despite severe LV dysfunction and borderline restrictive filling (DT: 150 ms, E/A >2). Dobutamine stress shows basal inferior ischemia and mid inferior biphasic response in **B**. Peak-dose (40 μg/kg/min) dobutamine response showed hypokinetic septal and lateral walls had deteriorated at peak dose, which is consistent with extensive ischemia **(C)**. CR = contractile reserve; DT = deceleration time; E/A = early-to-late diastolic filling ratio; HR = heart rate; other abbreviations as in Figure 2.

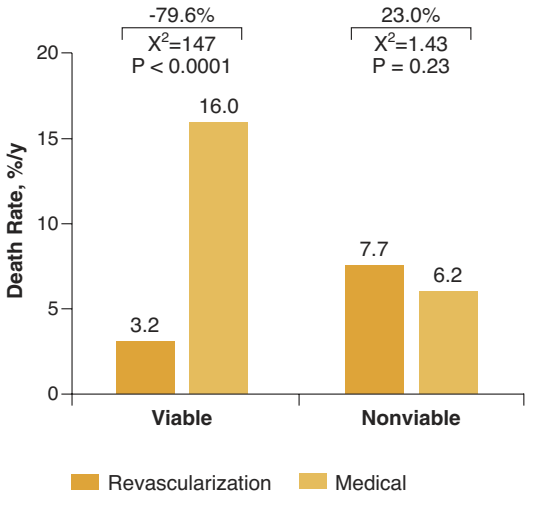


Figure 7. Prognostic Implications of Myocardial Viability Testing

The data are derived from meta-analysis of 3,088 patients with coronary artery disease and left ventricular dysfunction who underwent viability testing. Death rates for patients with and without myocardial viability treated by revascularization or medical therapy are shown. In patients with viable myocardium, there is 79.6% reduction in mortality among those who were treated with revascularization ($p < 0.0001$). In contrast, among patients without evidence of viable myocardium, there was no significant difference in mortality with revascularization versus medical therapy. Adapted, with permission, from Allman et al. (7).

also supplied by a stenosed infarct-related artery (Figs. 6A to 6C). The extent of viability is an important determinant of the likelihood of recovery of overall LV function (e.g., characterized by a LVEF improvement of >5%). The presence of >4 segments with a biphasic response has a specificity and sensitivity of 80% to 90% for prediction of global functional recovery. Patients demonstrating a significant LVEF improvement with LDDE are also likely to show global functional recovery and reverse remodeling (78).

Echocardiography is an ideal initial screening test in these patients, because of its wide availability, low cost, and similar levels of accuracy to other more expensive modalities (59). As with any noninvasive test, there may be false-negative and false-positive responses with LDDE. The reliability of LDDE is influenced by a number of other factors apart from the extent of viable tissue, and false-negative responses may be due to reduced substrate supply (compromised if the tissue is ischemic), loss of the myocardial contractile apparatus, and excessive fibrosis (which may splint the segment and prevent it from shortening). If flow is severely compromised, the tissue may become ischemic before exhibiting an augmentation response. For this reason, LDDE should be performed with multiple low doses (e.g., 5 and 10 μg/kg/min—some investigators have used a very low dose of 2.5 μg/kg/min and doses higher than 10 μg/kg/min), continually assessing the response, as augmentation may be very transient and ischemia is increasingly likely as the heart rate increases. The chronotropic response to dobutamine usually starts at doses >10 μg/kg/min, although the widespread use of long-acting beta blockers for heart failure has moved the low-dose threshold toward 20 μg/kg/min. Another cause of false-negative responses is damage to the contractile apparatus within viable myocytes, which is caused by recurrent episodes of ischemia and stunning. Failure to respond to dobutamine may not indicate lack of viability, which may still be identified using PET; in these situations, prolonged follow-up may be needed to demonstrate functional recovery after revascularization. Nontransmural scarring influences the likelihood of recovery of resting function and may cause false-positive responses. Subendocardial scarring is a major contributor to resting dysfunction, so segments with nontransmural scarring may respond to dobutamine because of augmentation of the subepicardium but not recover resting function after revascularization. There are risks in the performance of peak-dose dobutamine stress in individuals with severe LVD. The underlying reserve of the LV may be limited and hypotension, heart failure, and serious arrhyth-

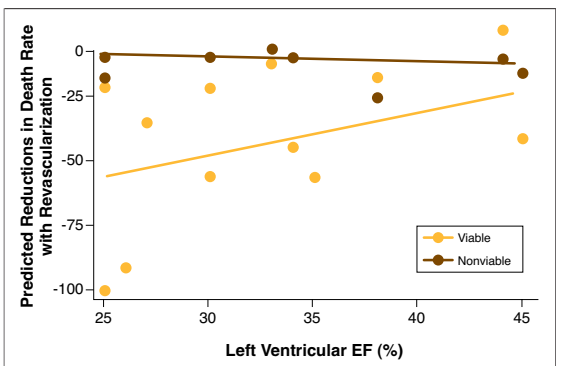


Figure 8. Myocardial Viability, LV Function, and Reduction in Mortality After Revascularization

The relationship of reductions in death rate to resting left ventricular ejection fraction in patients who had revascularization. In patients with nonviable myocardium, there is no reduction of death with revascularization. In patients with viable myocardium, the lower the ejection fraction, the greater the reduction of deaths after revascularization. Reprinted, with permission, from Allman et al. (7). Abbreviations as in Figure 2.

mias may ensue if severe ischemia develops. These tests should be performed by experienced personnel; the test may need to be stopped at the development of ischemia, and nitrates and oxygen may need to be administered. Nonetheless, there is no good evidence to indicate that there is a substantial increase of risk of dobutamine stress in the situation compared with the usual risk of a significant adverse event in 3 out of 1,000 studies.

A problem relates to the challenges of interpreting LDDE. As with all stress echocardiographic techniques, wall motion scoring is limited by subjectivity and technical challenges. The measurement of myocardial deformation may prove to be a more reliable means of quantitation of this response. Strain rate at LDDE correlates with the presence of myocardial viability evidenced by FDG imaging, with an optimal cut-point for this purpose being a strain-rate increment of >0.23/s (79). A strain-rate increment of >0.25/s also predicts functional recovery after revascularization (sensitivity 80%, specificity 75%) (80).

Magnetic resonance imaging. The demonstration of CR is an established predictor of myocardial viability (59). As with echocardiography, CMR assessment of CR is performed using the infusion of low doses of dobutamine (5 to 10 μg/kg/min). One study (49) compared low-dose dobutamine CMR to FDG PET in 35 patients with chronic MI and segmental LVD. Using both end-diastolic wall thickness and improvement in systolic thickening as markers of viability, CMR had a sensitivity, specificity, and diagnostic accuracy of 88%, 87%, and 92%, respectively. Using improvement in LV function post-revascularization as the reference standard in the same patient group (50), dobutamine CMR had a sensitivity and specificity of 89% and 92%.

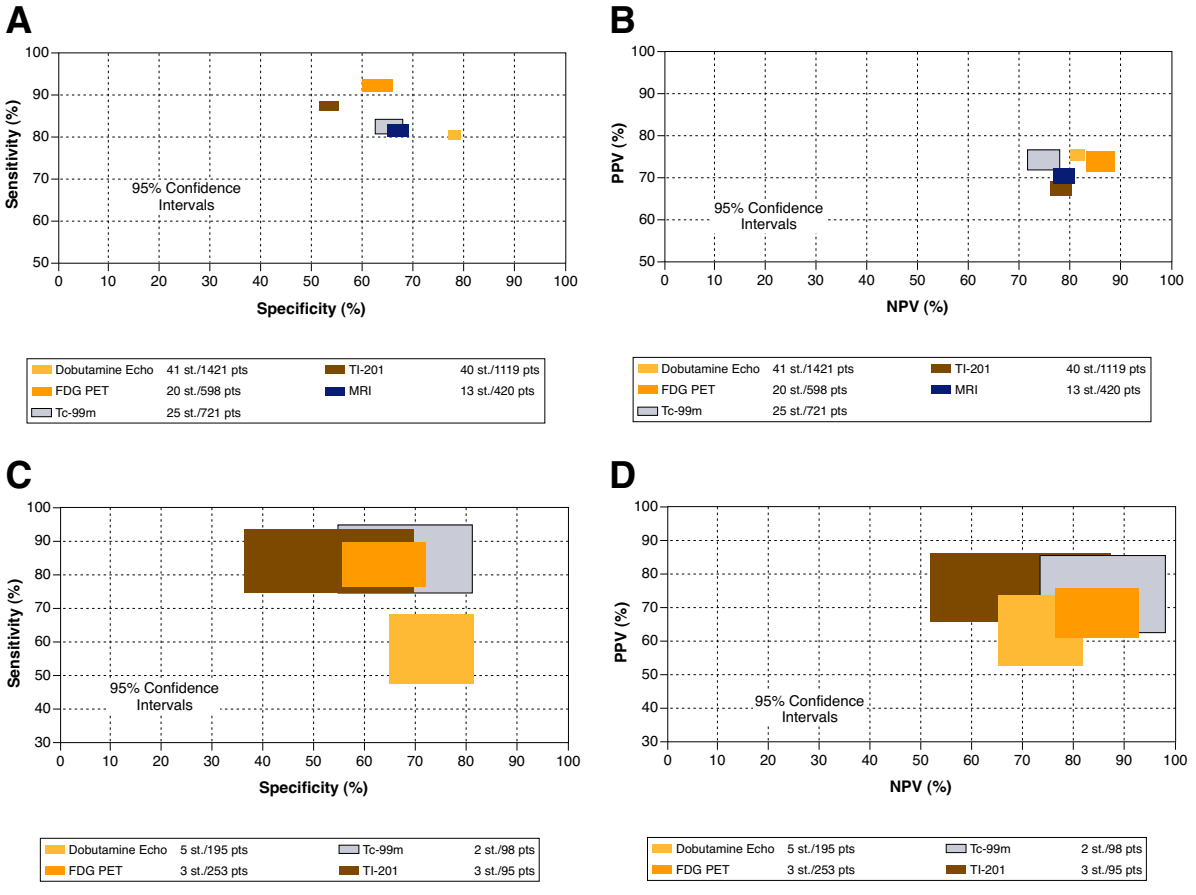


Figure 9. Diagnostic Accuracy of Various Techniques for Functional Recovery

Comparison of sensitivities and specificities **(A)** and predictive values **(B)** with 95% confidence intervals for the recovery of regional wall function. Comparison of sensitivities and specificities **(C)** and predictive values **(D)** of the various techniques with 95% confidence intervals for prediction of the recovery of global left ventricular function. Reprinted, with permission, from Schinkel et al. (86). FDG = ^{18}F fluorodeoxyglucose; NPV = negative predictive value; PPV = positive predictive value; pts = number of patients; st = number of studies; Tc-99m = Technetium-99m–labeled agents; T1-201 = thallium 201; other abbreviations as in Figures 2, 3, and 5.

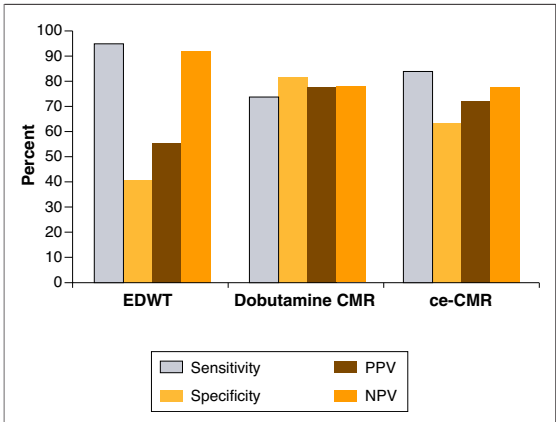


Figure 10. Diagnostic Accuracy of MRI for Post-Revascularization Improvement in Regional Function

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of data from various techniques with cardiac magnetic resonance (CMR). Figure developed from data of Schinkel et al. (86), with permission. ce-CMR = contrast-enhanced cardiac magnetic resonance; EDWT = end-diastolic wall thickness; other abbreviation as in Figure 3.

The utility of incorporating myocardial tagging for the assessment of intramyocardial functional reserve has also been demonstrated. In acute MI, the quantitative response to dobutamine is predictive of functional recovery, although the response in the subendocardium is quite complex (81). Studies in chronic ischemic heart disease before and after multivessel revascularization using tagged dobutamine CMR demonstrate that one-half of dysfunctional segments recover resting function, and, of the remainder, one-half demonstrate rest dysfunction but CR (82). One-half of these latter segments in turn recover rest function when examined 3 years after revascularization (82).

Some controversy exists as to which test performs best for predicting functional recovery among CMR-based techniques. Late gadolinium enhancement clearly identifies scarring, but the relationship between scarring and functional recovery in infarcts with 1% to 75% transmural infarction is complex. The performance of dobutamine CMR has been compared with LGE in this scenario (83). Although no difference was seen in the identification of viability in segments without LGE or those with scarring ≥75%, dobutamine CMR was superior in predicting recovery in zones in which LGE demonstrated between 1% and 75% transmural scarring (84). However, the performance of LGE varied greatly depending on the cutoff values used to define viability (84). Complementary use of dobutamine CMR and LGE may prove to be the optimal strategy for predicting post-revascularization functional recovery, as shown in a study (85) of 15 patients studied before and 20 weeks after coronary artery bypass surgery. In segments with 1% to 50% infarct transmurality, as shown by LGE, dobutamine response was predictive of functional recovery, whereas the predictive value of LGE alone was intermediate. Wall thickening with dobutamine CMR before revascularization correlated with wall thickening at rest at follow-up.

This combined approach to defining viability by CMR may be warranted in certain clinical scenarios. Although it may not be practical to perform low-dose dobutamine infusion on all

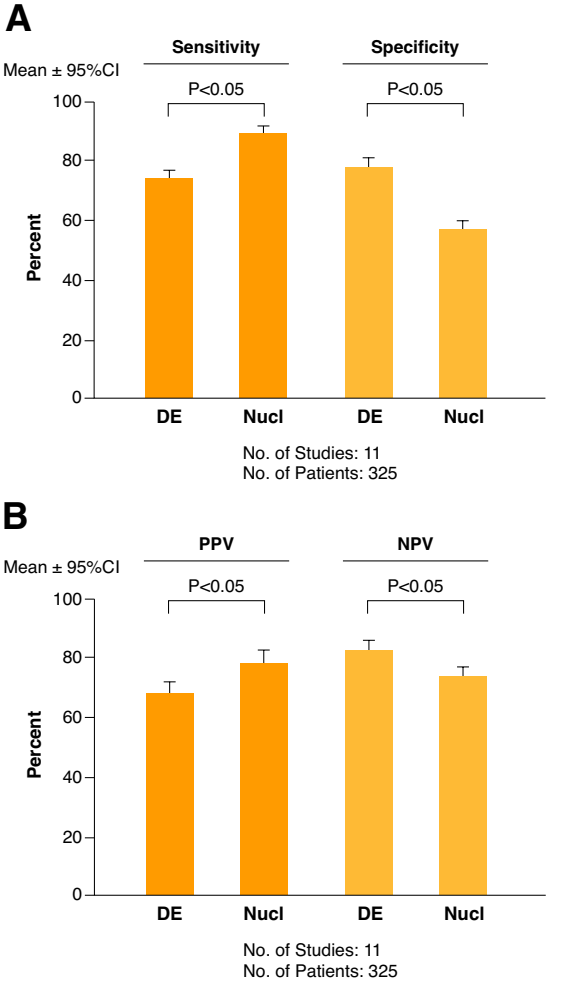


Figure 11. Comparison of Diagnostic Accuracy of Dobutamine Echocardiography and Nuclear Imaging

Sensitivity and specificity **(A)** and positive (PPV) and negative (NPV) **(B)** predictive value for predicting improvement in left ventricular function obtained by a direct comparison of dobutamine echocardiography (DE) and nuclear imaging (Nucl) of 325 patients in 11 studies. In each study, the same patients underwent both tests at the same medical center. Figure developed from data of Bax et al. (58), with permission.

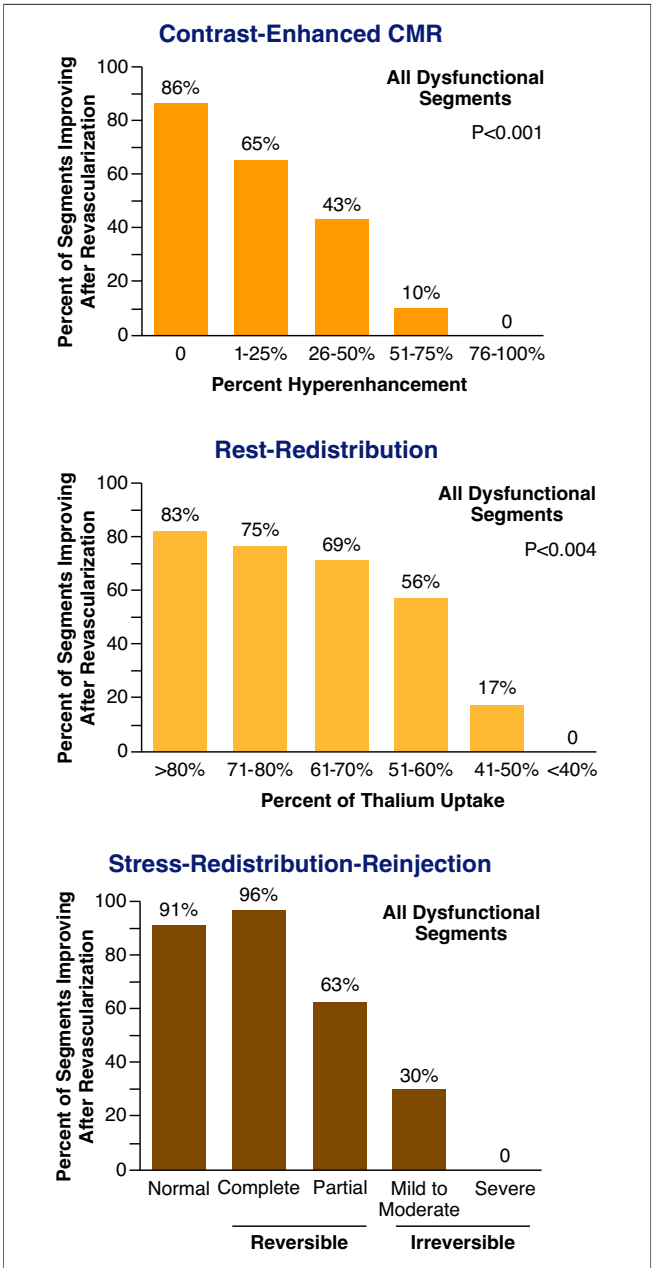


Figure 12. Comparison of Diagnostic Accuracy of Nuclear and Magnetic Resonance Imaging for Functional Recovery After Revascularization

Relationships between recovery of function after revascularization with contrast-enhanced cardiac magnetic resonance, and 2 thallium protocols optimized for viability detection: 1) rest-redistribution and 2) stress-redistribution-reinjection imaging are shown. Irrespective of the imaging modality applied, the data suggest that recovery of function after revascularization is a continuum and is coupled to the ratio of viable to scarred myocardium within dysfunctional myocardial segments. The extent of infarct size on CMR or percentage of thallium defect on SPECT correlated with decreasing likelihood of functional recovery after revascularization. Reprinted, with permission, from Dilsizian (88).

patients evaluated for viability, those patients with multiple segments having 1% to 50% transmurality may benefit from this decision. In patients with no late enhancement or >50% late enhancement, there is little to gain by adding dobutamine, and LGE remains the preferred technique because of its ease of use.

Prognostic Implications of Myocardial Viability Testing

Beyond the assessment of mere presence or absence of myocardial viability and predictive values of the various tests for recovery of regional or global LV function, it is perhaps equally important (if not more important) to demonstrate a survival advantage offered by revascularization for patients with ischemic LVD with viable myocardium. In a pooled analysis consisting of 3,088 patients in 24 studies, long-term survival after revascularization or medical therapy was determined independent of the type of viability testing, which included SPECT radionuclide imaging, PET, or dobutamine echocardiography (7). In patients exhibiting predominantly viable myocardium, follow-up on medical therapy was associated with very high risk, a 16% annual mortality. On the other hand, in similar patients, revascularization was associated with an 80% reduction in annual mortality (16% vs. 3.2%, $p < 0.0001$), compared with medical therapy (Fig. 7). Importantly, patients with the most severe LVD derived the greatest benefit from revascularization (Table 1). With worsening LVEF, the survival benefit associated with revascularization of patients with viable myocardium increased proportionately (Fig. 8) (7).

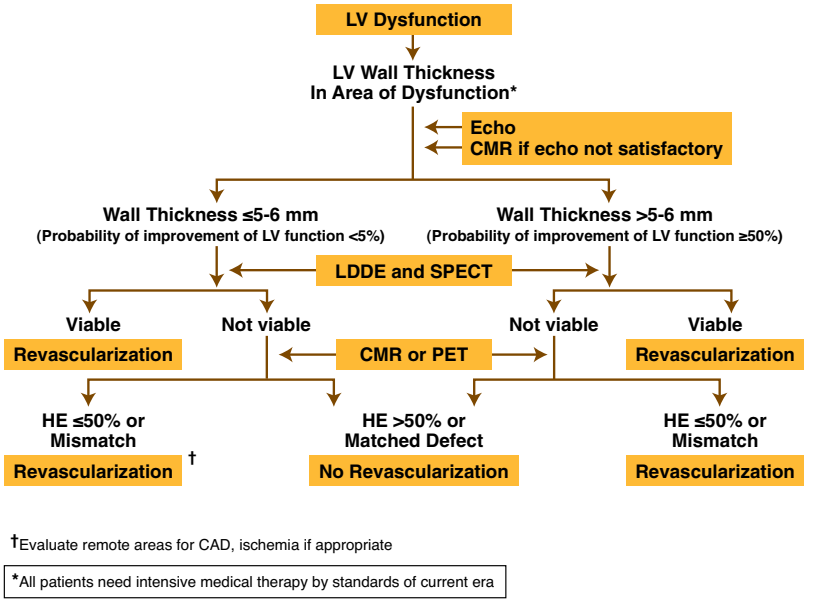
Integrated Imaging in Clinical Practice

None of the currently available imaging tools can address all the different aspects of the complex pathophysiology of myocardial viability and hibernation. Accordingly, they should often be used in combination to achieve the highest possible level of diagnostic accuracy. The clinician and noninvasive imager should note the following in the evaluation of reversible ischemic dysfunction:

- The sensitivity, specificity, positive predictive, and negative predictive values of the various tests for recovery of regional LV function and for

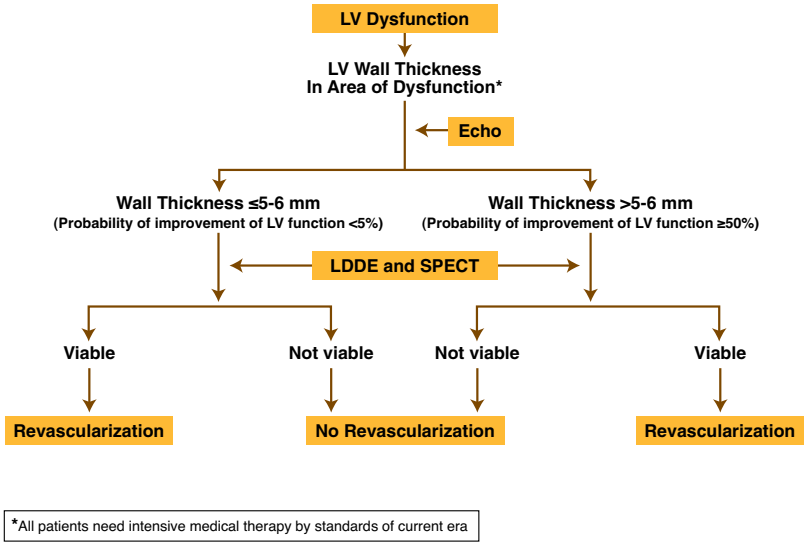
recovery of global LV function (Figs. 9A to 9D, Fig. 10) (86).

- These studies included various methodologies, patient populations, and end points and thus should be interpreted with appropriate caution. Data obtained by direct comparison of dobutamine echocardiography and nuclear studies in the same patients in the same centers are shown in Figures 11A and 11B (58).
- Single-photon emission computed tomography imaging with thallium-201 or technetium-99m perfusion tracers is more sensitive for detecting viable myocardium than dobutamine echocardiography. Low-dose dobutamine echocardiography is more specific for predicting recovery of function after revascularization. Thus, markers of CR predict functional recovery with greater specificity than do markers of preserved cell membrane function (87). The recommended SPECT imaging is stress-redistribution-reinjection. It provides information about viability and ischemia. For those who cannot undergo stress imaging, rest-redistribution can be used.
- The retrospective nature of all available studies represents a weakness in the collective evidence base. These are the only data that are available and one should exercise some care in their application to patient management. However, it should be recognized that prospective, properly designed and executed studies will likely not be available for a considerable period. Moreover, the Schinkel et al. review (86), from which Figures 9A to 9D and Figure 10 are shown, was comprehensive and included all available studies with adequate data and follow-up. This allows for a reasonable, and probably a very good, plan of decision making for patient management at the present time.
- There is no perfect test (95% to 100% sensitive and specific), and therefore, there may be a need for combination of tests.
- The judgment to use test(s) at any 1 medical center depends on the availability of the test(s) and the skill and experience in performing the test(s) and interpreting the results.
- Mild-to-moderate improvement/severe defect on reinjection, ≤50% of thallium uptake on SPECT imaging, and >50% LGE on CMR indicate a small probability of LV function improvement after revascularization (Fig. 12) (88).
- The patients should *first* have an echocardiogram/Doppler (or another test) to diagnose LVD.
- A suggested format for diagnosis of viable myocardium and need for myocardial revascularize-



Algorithm 1.

CAD = coronary artery disease; CMR = cardiac magnetic resonance; ECHO = echocardiogram/Doppler; HE = hyperenhancement; LDDE = low-dose dobutamine echocardiography; LV = left ventricular; PET = positron emission tomography; Revasc = myocardial revascularization by PCI/CABG if technically feasible; SPECT = single-photon emission computed tomography; Viable = hibernating myocardium.



Algorithm 2.

Abbreviations as in Algorithm 1.

tion if coronary arteries are suitable is shown in Algorithm 1. The format of the proposed studies is the one which uses tests that are available at larger medical centers and there is good volume of data documenting the value of the tests.

- A simplified format that proposes studies that are most widely available to most practicing clinical cardiologists is shown in Algorithm 2.
- Criteria suggesting LV function is not likely to improve with revascularization are listed in Table 3.

Table 3. Patients With Global LVD and Multivessel Disease

Criteria indicating LV function with low probability of improvement with revascularization
• Major criteria:
LVWT ≤5 to 6 mm
No response to LDDE
SPECT negative for viability
CMR: LGE >50%
PET: negative for HM
• Minor criteria:
LVEF ≤0.20
LV volumes: 1 or more of the following:
By angiography: LVEDVI ≥200 ml/m^2 and/or LVESVI ≥120 ml/m^2
By echocardiography: LVEDVI ≥170 ml/m^2 and/or LVESVI ≥90 ml/m^2
Echocardiographic dimension: LVEDDI ≥5.5 cm^2/m^2
Criteria indicating LV function not likely to improve with revascularization:
• ≥4 major
• 3 major plus 1 minor
• 2 major plus 2 minor

CMR = cardiovascular magnetic resonance; EDV/EDVI = end-diastolic volume/index; EF = ejection fraction; ESV/ESVI = end-systolic volume/index; HM = hibernating myocardium; LDDE = low-dose dobutamine echocardiography; LGE = late gadolinium enhancement; LV = left ventricle; LVD = left ventricular dysfunction; PET = positron emission tomography; SPECT = single-photon emission computed tomography; WT = wall thickness.

Clinical Decision Making

There are several steps in the management of these patients:

- There is a need for almost immediate diagnosis of LVD in the clinical syndromes described earlier in this report. Usually, this is best done by echocardiography/Doppler studies.
- Appropriate test(s) for viability (± ischemia) should be performed very early in the management of these patients. Test(s) for viability and coronary arteriography are essential prior to a consideration for revascularization.
- The entire clinical picture, including results and proper interpretation of the results of diagnostic tests, should be incorporated into clinical decision making.

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